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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,270	09/05/2003	Fritz Eckstein	00-838-Q	7134

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,270	ECKSTEIN ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 9-5-03.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3-26-04, 4-5-04, 4-19-04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Pending Claims

Claims 1-26 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to RNA molecules comprising 2'-deoxy-2'-fluoro nucleotides that are between about 12 and about 36 nucleotides in length (claims 1-13 and 24-26) and methods of increasing the stability of RNA molecules by introducing 2'-deoxy-2'-fluoro nucleotides (claims 14-23).

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

In the instant case, the breadth of claims 1-13 and 24-26 embraces any RNA molecules with length limitation of 12 to 36 nucleotides. Since the claims do not contain any other positive recitations of structural limitation except for the length limitation of the RNA molecules, claims 1-13 and 24-26 read broadly on any short RNA molecules such as RNA antisense oligonucleotides, hairpin ribozymes, hammerhead ribozymes, RNA aptamers, short interfering RNA molecules, and so forth. Although the instant specification discloses five species of 2'-deoxy-2'-fluoro-modified ribozyme RNA molecules (identified as E2, RE115 (FC), RE115 (FU), RE115 (FU,S), RE115 (FC, FU, S)), the 2'-modified ribozyme molecules disclosed therein are not representative of the genus of RNA molecules encompassed by the broadly claimed RNA molecules in claims 1-13 and 24-26.

The breadth of claims 14-23 embraces methods of increasing the stability of RNA molecules by introducing 2'-deoxy-2'-fluoro nucleotides, wherein said RNA molecules, as claimed, harbor no structural limitations due to the total lack of any recitation of the RNA molecule structures. Thus, the instantly claimed invention reads broadly on methods of increasing the stability of any RNA molecules, regardless of size limitations. As stated above, the instant specification exemplifies only short RNA ribozyme molecules. Since the instant claims are drawn to methods of increasing stability of any RNA molecules, adequate written description requires more than the species provided in the specification. Therefore, it is concluded that the five ribozyme molecules disclosed in the instant specification are not representative of the genus encompassed by the broadly claimed RNA molecules recited in claims 14-23.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555. 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (see page 1117).

Claims 14-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of increasing the stability of an RNA molecule comprising 2'-deoxy-2'-fluoro uridine nucleotides as represented by E2 or an RNA molecule comprising 2'-deoxy-2-fluoro uridines, cytosines and phosphorothioates as represented by RE115 (FC, FU, S), does not reasonably provide enablement for methods of increasing the stability of RNA molecules comprising 2'-deoxy-2'-fluoro cytidines, adenosines, and guanosines. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth

of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the instant case, the methods of increasing stability of RNA molecules by introducing 2'-deoxy-2'-fluoro nucleotides were considerably nascent at the time the instant invention was made when the foreign priority application (PCT/EP90/01731) was filed in October, 1990.

Since the state of the prior art as well as the level of predictability in the art regarding the instantly claimed subject matter were not firmly grounded at the time the invention was made, as originally filed in 1990, the amount of direction provided by the inventor such as working examples for the claimed subject matter should be sufficient to guide a person of ordinary skill in the art to practice the claimed invention without undue experimentation.

Although the instant specification provides working examples for methods of increasing stability of a ribozyme (identified as E2) comprising 2'-deoxy-2'-fluoro uridines (Example 2 and Figure 3) or a ribozyme (identified as RE115 (FC, FU, S)) comprising a combination of 2'-deoxy-2'-fluoro uridines, cytidines, and phosphorothioates (Example 5), it does not exemplify methods of increasing stability of RNA molecules comprising 2'-deoxy-2'-fluoro cytidines, adenosines, and guanosines. Since methods of increasing stability of RNA molecules were neither routine nor predictable at the time the instant invention was made, undue experimentation would have been necessary in order for one skilled in the art to practice the instantly claimed invention. Accordingly, the invention commensurate in scope with claims 14-23 is not enabled.

Double Patenting

Claims 1-13 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 25 of U.S. Patent No. 5,672,695 in view of U.S. Patent No. 5,264,564. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instantly claimed subject matter is embraced by the scope of the claimed subject matter in the U.S. Patent No. 5,672,695.

The instant claims claim RNA molecules between about 12 and about 36 nucleotides in length comprising at least one 2'-deoxy-2'-fluoro nucleotide, further comprising at least one phosphorothioate linkage.

The U.S. Patent No. 5,672,695 claims recite RNA molecules with catalytic activity comprising at least one modified nucleoside, wherein the hydroxyl group at the 2'-position of the ribose sugar is replaced by a fluoro group. In particular, claim 25 recites an RNA molecule comprising 2'-deoxy-2'-fluoro uridines.

The disclosure of U.S. Patent No. 5,264,564 teaches that modified DNA or RNA oligonucleotides, especially short antisense oligonucleotides, with phosphorothioates confer enhanced stability against endonucleases (column 1, lines 63-68; column 2, lines 1-4).

In view of the foregoing, it would have been obvious to one of ordinary skill in the art at the time the instantly claimed invention was made to make short RNA molecules comprising at least one 2'-deoxy-2'fluoro nucleotide as claimed in the U.S. Patent No. 5,672,695, further comprising at least one phosphorothioate linkage as taught by the disclosure of U.S. Patent No. 5,264,564. One of ordinary skill in the art would have been motivated to modify cytidine,

adenosine, and guanosine nucleotides with 2'-deoxy-2'-fluoro nucleotides because an RNA molecule comprising 2'-deoxy-2'-fluoro uridines was already claimed and known at the time the instantly claimed invention was made. The skilled artisan would have been motivated to so with a reasonable expectation of success because cytidine, adenosine, guanosine, and uridine are all species of nucleotides and the patented success of making RNA molecules with 2'-deoxy-2'-fluoro uridines would render making RNA molecules with 2'-deoxy-2'-fluoro cytidines, adenosines, and guanosines obvious. Moreover, the skilled artisan would have been motivated to further modify the RNA molecules with 2'-deoxy-2'-fluoro nucleotides by substituting phosphodiester linkages with phosphorothioates for enhanced stability as taught by U.S. Patent No. 5,264,564, thereby achieving additive stability effects by combining the 2'-deoxy-2'-fluoro nucleotides with phosphorothioates. Accordingly, the instantly claimed invention is *prima facie* obvious over claims 1-6 and 25 of U.S. Patent No. 5,672,695 in view of the disclosure of U.S. Patent No. 5,264,564.

Claims 1-8, 11-13, and 24-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 25 of U.S. Patent No. 5,672,695 in view of U.S. Patent No. 5,144,019. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instantly claimed subject matter is embraced by the scope of the claimed subject matter in the U.S. Patent No. 5,672,695.

The instant claims claim RNA molecules between about 12 and about 36 nucleotides in length comprising at least one 2'-deoxy-2'-fluoro nucleotide, wherein the RNA molecules are complementary to HIV RNA.

The U.S. Patent No. 5,672,695 claims do not specifically claim RNA molecules having nucleic acid sequences complementary to HIV RNA.

Rossi et al. (U.S. Patent No. 5,144,019) claim synthetic catalytic RNA ribozyme molecules targeted to a region of HIV-1 RNA. See claims 1-3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make RNA molecules comprising 2'-deoxy-2'-fluoro nucleotides as claimed in the U.S. Patent No. 5,672,695, wherein said RNA molecules target HIV RNA as claimed in the U.S. Patent No. 5,144,019. One of ordinary skill in the art would have been motivated to make RNA molecules targeted to HIV RNA with a reasonable expectation of success because it was an art-recognized goal to target HIV RNA with short RNA molecules as evidenced by the claims of Rossi et al.' patent. Accordingly, the instantly claimed invention is *prima facie* obvious over claims 1-6 and 25 of U.S. Patent No. 5,672,695 in view of claims 1-3 of U.S. Patent No. 5,144,019.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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